UNIVERSITY OF CALIFORNIA, SAN DIEGO

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DEPARTMENT OF PSYCHIATRY
SCHOOL OF MEDICINE

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LA JOLLA, CALIFORNIA 92093

January 31, 1989

Joel Davis, Ph.D.
Department of the Navy
Office of Naval Research
Arlington, VA 22217-4744

Dear Dr. Davis:

This letter will provide you with the final technical report of research accomplished during the tenure of contract N00014-85K-0699 which terminated 6-30-88 and was entitled The Neurophysiological and Neuroanatomical Organization of the Subcortical Motor System, with Special Reference to the Functional Organization of Peptides within the Basal Ganglia. The publications supported by this award as well as invited lectures and symposium presentations by the principal investigator are listed at the end of the narrative.

We have performed experiments over the past three years directed at understanding the neurophysiological and neuroanatomical principles underlying the mechanisms involved in the production of voluntary movements, especially those mechanisms engaged by the neostriatum of the brain of mammals. We have been concerned particularly with the dopaminergic system which projects to the neostriatum and the efferent system of the neostriatum which projects to the substantia nigra of the brainstem. ~~Of course,~~ the dopamine system connection to substantia nigra and neostriatum is well known for its involvement in the deterioration of voluntary movement as seen in victims of Parkinson's disease and it's associated symptoms of rigidity, tremor and bradykinesia.

~~Indeed~~, a number of disorders of voluntary movement involve the pathology or dysfunction of the neostriatum and its associated afferent systems and efferent targets, including the substantia nigra. Our initial efforts focussed both on the GABA-utilizing efferent projections of the neostriatum which we were able to identify and characterize using antidromic stimulation (Ryan et al., 1986) and dopamine neurons of substantia nigra in the rat brain model system which we both identified neurophysiologically and later labelled utilizing intracellularly- injected

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horseradish peroxidase (Tepper et al., 1987). We were able to shed considerable light on both of these projection systems including the development of an entirely new conception of antidromic responses of neostriatal efferent projection neurons which had previously been identified as orthodromically activated neostriatal interneurons. In addition, intracellular labelling and careful light microscopic observations of the dopaminergic neurons resulted in a variety of insights concerning the anatomical nature of these cells including new knowledge that the dendrites of these neurons were much longer and covered a much greater territory than heretofore believed. In addition, we established a variety of neuro-physiological and neuroanatomical correlations at the light and electron microscopic levels which will be the subject of several future publications. Our neurophysiological methodology yielded an important new method for identifying the fact that antidromically-activated neurons had branched or unbranched axon trajectories (Klemfuss et al, 1987).

In addition to this work, we have completed the development (Young et al., 1987; Kinnamon et al., 1989) and application of computer-assisted three dimensional reconstruction for both electron microscopic as well as light microscopic images from serial electron and light micrographs. One particularly important result of the application of this technology was to reveal that staining of individual striosomes for the neuropeptide enkephalin in the mammalian neostriatum was actually staining a rather complex and intricate network in the neostriatum when individual striosomes were entered into the computer and the entire three dimensional array of the enkephalin staining was visualized with immunocytochemically stained serial sections (Groves et al., 1988a; Martone et al., 1987). As you know, our three dimensional reconstruction of this neostriatal network appeared on the cover of the Journal of Neuroscience in March, 1988.

We are now attempting the integrate the three dimensional pattern of striosomal markers with choline acetylase-rich neuronal somata since a key element in the information processing matrix of the neostriatum consists of cholinergic interneurons and their interaction with peptide-containing compartments of the mammalian neostriatum. Other neuroanatomical studies accomplished during this reporting period include studies of cholinergic neurons of the brainstem important in the regulation of REM sleep (Shiromani et al., 1987). As you may know, the interaction of dopamine and acetylcholine is considered an important parameter of function of the neostriatum and its control of voluntary movement. In other studies we are very interested in and are pursuing now the relevance of presynaptic receptor systems on afferents to neostriatum including dopaminergic terminals (Groves et al., 1988b) as well as heteroreceptors on the terminals of other systems projecting into the

neostriatum such as the glutamatergic projections from cerebral cortex or the serotonergic projections from the brainstem. We believe that the information processing functions of the neostriatum rely in significant ways on the modulation of incoming information by presynaptic autoreceptors and heteroreceptors.

Publications and presentations of research during this reporting period:

ARTICLES IN SCIENTIFIC JOURNALS

Ryan, L.J., Young, S.J., & Groves, P.M. Substantia nigra stimulation evoked antidromic responses in rat neostriatum. Experimental Brain Research 63: 449-460, 1986.

Tepper, J.M., Sawyer, S.F., & Groves, P.M. Electrophysiologically identified nigral dopaminergic neurons intracellularly labeled with HRP: Light microscopic analysis. Journal of Neuroscience 7(9): 2794-2806, 1987.

Shiromani, P.J., Armstrong, D.M., Bruce, G., Hersh, L.B., Groves, P.M., & Gillin, J.C. Relation of pontine choline acetyltransferase immunoreactive neurons with cells which increase discharge during REM sleep. Brain Research Bulletin 18: 447-455, 1987.

Klemfuss, H., Young, S.J., & Groves, P.M. Do antidromic latency jumps indicate axonal branching in nigrostriatal and hypothalamo-neurohypophysial neurons? Brain Research 409: 197-203, 1987.

Young, S.J., Royer, S.M., Groves, P.M., & Kinnamon, J.C. Three-dimensional reconstruction from serial micrographs using the IBM PC. Journal of Electron Microscopic Techniques 6: 207-217, 1987.

Groves, P.M., Martone, M., Young, S.J., & Armstrong, D.M. Three-dimensional pattern of enkephalin-like immunoreactivity in the caudate nucleus of the cat. Journal of Neuroscience 8(3): 892-900, 1988a.

Gariano, R.F. and Groves, P.M. Burst firing induced in midbrain dopamine neurons by stimulation of the medial prefrontal and anterior cingulate cortices. Brain Research 462: 194-198, 1988.

BOOKS, CHAPTERS, AND MONOGRAPHS

Groves, P.M., & Young, S.J. Neurons, networks and behavior: An introduction. IN: J.O. Cavenar, Jr. (Ed.), Psychiatry--Volume 3, Section 2: Psychobiological Foundations of Clinical Psychiatry. Philadelphia: J.B. Lippincott, 1985, pp. 1-19.

Judd, L.L., & Groves, P.M. (Eds.) Psychobiological Foundations of Clinical Psychiatry, Volume 3, Section 2 of Psychiatry (Cavenar). Philadelphia: J.B. Lippincott, 1985.

Tepper, J.M., Nakamura, S., & Groves, P.M. Noradrenergic terminal excitability: Effects of presynaptic receptor stimulation and blockade. IN: J.J. Feigenbaum & M. Hanani, The Presynaptic Regulation of Neurotransmitter Release. London, Tel Aviv: Freund, in press, 1987.

Tepper, J.M., Nakamura, S., & Groves, P.M. Dopaminergic and serotonergic terminal excitability: Effects of autoreceptor stimulation and blockade. IN: J.J. Feigenbaum & M. Hanani, The Presynaptic Regulation of Neurotransmitter Release. London, Tel Aviv: Freund, in press, 1987.

Groves, P.M., & Rebec, G.V. An Introduction to Biological Psychology, 3rd Edition. Dubuque, Iowa: W.C. Brown, 1988.

Groves, P.M., Ryan, L.J., & Martone, M.E. Dopamine regulation of neostriatal input/output relations. IN: Progress in Catecholamine Research, Part B: Central Aspects. New York, New York: Alan R. Liss, pp. 124-129, 1988b.

Rebec, G.V. and Groves, P.M. Instructor's Resource Manual/Test Item File for An Introduction to Biological Psychology, 3rd Edition (Groves & Rebec). Dubuque, Iowa: W.C. Brown, 1988.

Tepper, J.M., & Groves, P.M. Study Guide to Accompany An Introduction to Biological Psychology, 3rd Edition (Groves & Rebec). Dubuque, Iowa: W.C. Brown, 1988.

Kinnamon, J.C., Royer, S.M., Young, S.J., Martone, M. and Groves, P.M. The application of IBM PC-based three-dimensional reconstructions to structural biology. Proceedings of National Computer Graphics Association Conference, in press, 1989.

BOOK REVIEWS

Groves, P.M. Review of "Chemoarchitecture of the Brain," by R. Nieuwenhuys. Contemporary Psychology 32: 943-944, 1987.

Groves, P.M. Review of "The Dopaminergic System," by E. Fluckiger, E.E. Muller, & M.O. Thorner (Eds.). Contemporary Psychology 32: 470-471, 1987.

ABSTRACTS

Shiromani, P.J., Armstrong, D., Berkowitz, A., Bruce, G., Hersh, L.B., Groves, P.M., & Gillin, J.C. The distribution of choline acetyltransferase (ChAT) immunoreactive neurons in the feline brainstem: Relation to areas implicated in REM sleep generation. Sleep Research 16: 31, 1987.

Martone, M., Groves, P.M., Young, S.J., & Armstrong, D.M. Three-dimensional distribution of cholinergic perikarya in the neostriatum of adult cats. Society for Neuroscience Abstracts, p. 1573, Seventeenth Annual Meeting, New Orleans, Louisiana, November 16-21, 1987.

Shiromani, P.J., Berkowitz, A., Armstrong, D.M., Groves, P.M., & Gillin, J.C. Neurons from the peribrachial region project to the medial PRF: WGA-HRP and fluorescence study in the cat. Society for Neuroscience Abstracts, p. 1657, Seventeenth Annual Meeting, New Orleans, Louisiana, November 16-21, 1987.

Tepper, J.M., Sawyer, S.F., & Groves, P.M. Ultrastructure and synaptic contacts of electrophysiologically identified nigral dopaminergic and non-dopaminergic neurons intracellularly labeled with HRP. Society for Neuroscience Abstracts, p. 1572, Seventeenth Annual Meeting, New Orleans, Louisiana, November 16-21, 1987.

INVITED LECTURES AND SYMPOSIA

August 21, 1986
Brain and Behavior Symposium
Office of Naval Research
San Diego, California

October 16, 1986
Center for Cell Biology
Sinai Hospital of Detroit
Detroit, Michigan

January 13, 1987
Neurosciences Lecture Series
University of California, San Diego
La Jolla, California

January 30, 1987
Department of Psychobiology
University of California, Irvine
Irvine, California

June 15, 1987
Sixth International Catecholamine Symposium
Jerusalem, Israel

September 17, 1987
Symposium on Haptics and Sensory Guided Motor Control
Office of Naval Research
National Academy of Sciences Woods Hole Study Center
Woods Hole, Massachussetts

October 2, 1987
Invited Address
Minority Access to Research Careers
NIH Centennial Symposium
Washington, D.C.

September 16, 1988
Invited Presentation
Neurosciences Seminar Series
Scripps Clinic and Research Foundation
La Jolla, California

November 9, 1988
Program in Neuroscience
University of Southern California
Los Angeles, California

November 16, 1988

Slide Session Chairman, "Dopamine Receptors II"
Society for Neuroscience Meeting
Toronto, Canada

Sincerely,

Philip M. Groves, Ph.D.
Professor of Psychiatry
and Neuroscience